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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/841,091	04/23/2001	Athan Kuliopulos	18475-034 (NEMC-215)	4965

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EXAMINER	
WEGERT, SANDRA L	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/841,091	KULIOPULOS ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6,10-14,19,29,31 and 35-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,10-14,19,29,31 and 35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/15/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Declaration of Dr. Kuliopulos under 37 CFR 1.132, filed 15 January 2004, has been entered into the record. The Amendment and Information Disclosure Statement, both submitted 15 January 2004, have been entered. Claims 5, 7-9, 15-18, 20-28, 30 and 32-34 are canceled. Claims 1-4, 14 and 19 are amended. Claims 1-4, 6, 10-14, 19, 29, 31 and 35-43 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a previous Office action.

Withdrawn Objections and/or Rejections

URL's

The objection to the disclosure for reciting browser-executable code (30 September 2003) is *withdrawn.* Applicants amended the Specification to remove all reference to URL's and other browser-executable text (15 January 2004).

Claim Objections

The objection to Claims 3, 4, 8 and 19 for reciting non-elected inventions (page 3, 30 September 2003) is *withdrawn.* Claim 8 has been cancelled (15 January 2004). Applicants also pointed out that the recited receptors and lipids are species and that, therefore, it is improper to object to their recitation in a claim (page 8, 15 January 2004).

Claim Rejections - 35 USC § 112, first paragraph – Written Description

The rejection of Claims 1-3, 4, 6, 10-14, 19, 29 and 31 for reciting "intracellular portions of G-protein coupled receptors" or a "hydrophobic moiety," as set forth at page 5-7 of the previous Office Action (30 September 2003), is *withdrawn.* Applicants amended Claims 1, 3, 4, 14 and 19 to add references to specific portions of G-protein coupled receptors, as well as encompassed lipids (15 January 2004).

Maintained Objections and/or Rejections

35 USC § 112, First Paragraph – Scope of Enablement

The rejection of Claims 1-4, 6, 10-14, 19, 29, 31 and 35-43, under 35 U.S.C. 112, first paragraph, for improper Scope of Enablement, is *maintained.* The specification is enabling for a pepducin constructed from the third intracellular loop of the PAR4 receptor, comprising the sequence TLAASG...RRY (SEQ ID NO: 9) and attached to the fatty acid palmitate. It is not enabling for chimeric peptides comprising portions of G protein-coupled receptors other than the third intracellular loop of PAR4, or of other domains of similar or dissimilar G protein-coupled receptors, or of the PAR4 pepducin of SEQ ID NO: 9 attached to a hydrophobic moiety other than palmitate. This rejection was previously made at pages 3-5 of the previous Office Action (30 September 2003).

Claims 1-4, 6, 10-14, 19, 29, 31 and 35-43 are drawn to chimeric peptides comprising intracellular portions of a G protein-coupled receptor coupled with hydrophobic moieties,

provided the peptide portion of the chimera does not comprise a native extracellular ligand. Dependent claims recite linear fatty acid residues that are 8 to 18 carbons in length, a peptide comprising intracellular portions of receptors other than PAR1 and compositions comprising the pepducins.

The specification discloses *pepducins* constructed from the third intracellular loop of the PAR1 receptor, comprising the sequence TLAASG...RRY (SEQ ID NO: 9) and attached to palmitate. Data is presented that demonstrate the pepducins constructed from this sequence of the third intracellular loop, and attached to hydrophobic moieties, interact *intracellularly* with the G -proteins associated with a specific receptor, generally inhibiting the expected cellular response. For example, pepducins acting at the platelet-aggregation receptors (PAR) inhibit inositol triphosphate production and subsequent platelet aggregation (Specification, Figures 4C and 4D). Additionally, P1pal-13 (the elected invention comprising SEQ ID NO: 9) and P1pal-19 were tested for specificity at their cognate receptors versus other G-protein-coupled receptors (Specification, Example 3, paragraphs 121 and 122). Additionally, the Declaration of Dr. Kuliopulos under 37 CFR 1.132, (15 January 2004) lists experiments in which additional pepducins derived from PAR1 and PAR4, and comprising fatty acids, were tested for their abilities to inhibit platelet aggregation (Declaration, Figure G). The Declaration also lists the results of Ca^{2+} fluorescence (correlated with intracellular transduction) using pepducins comprising sterols rather than fatty acids (Declaration, Figure I).

However, a sufficient amount of direction or guidance is lacking in Claims 1-4, 6, 10-14, 19, 29, 31 and 35-43 as far as specifying the peptide/fatty acid member that has the binding characteristics and physiological function of P1pal-13 (see Table 1, Specification). The numbers

and types of pepducins that can be formed from the claimed G protein-coupled receptor fragments are very large, as well as highly-variable in their physiological effects (see Specification, Table 1 and Kuliopulos Declaration, Figures E through I).

It is noted that at pages 8-12 of the Response (15 January 2004) that Applicant cites pertinent case law reviewing the legal standard of enablement, and discusses the changes made in the pending claims (page 10). The Examiner takes no issue with Applicant's general comments regarding the legal standard for enablement. The Applicant argued (page 13, 15 January 2004) that:

> The data described in the specification and in [of] Dr. Kuliopulos' declaration indicate that PAR1 i3 loop-based peptide myristic, palmitic, cholanic, lithocholic, cholic, and lauric, derivatives, along with PAR4 P4-10 cholanic, lithocholic, palmitic, myristic, and stearic derivatives are capable of inhibiting platelet aggregation. This inhibitory activity is not limited to PAR4, nor is it limited to palmitate. The data described in the specification and Dr. Kuliopulos' declaration also shows that the stimulatory effect on platelet aggregation shown by Plpal-19 and P1pal-13 is not limited to palmitate, but also is effective when these shortened PAR1 peptides are linked to lithocholate, myristate, deoxycholate, cholate, caprylate, or laurate.

Applicant's arguments have been fully considered but are not deemed persuasive for the following reasons:

While the examiner agrees that all or most pepducins produced by the disclosed methods have been shown to be enabled in terms of their interactions with native receptors, each pepducin produced is quite unique in its effects. The instant Specification at Table 1, for example, as well as the Kuliopulos Declaration (15 January 2004, Figures E through I, for example) list results of platelet aggregation or Ca^{2+} fluorescence using many combinations of peptides and lipids comprising the pepducins. All give unique results in terms of affinity, the ability to transduce a response and receptor specificity. This is not surprising given that each lipid differs in its ability to pass through cell membranes, and each peptide will act differently at each receptor. This is

exemplified in Table 1 of the Specification which shows that even pepducins derived from PAR1 (SEQ ID NO's 1-6) each have unique binding and transductional characteristics. Therefore, even though exemplary numbers of pepducins were made and tested, each is unique in its effects and must be claimed with reference to both SEQ ID NO and lipid comprising.

Analysis of the Wands factors was provided in the previous Office Action (30 September 2003). Due to the large quantity of experimentation required to determine how to make all possible chimeric proteins that have the characteristics of being made from a G protein-coupled receptor but not comprising a natural ligand, the lack of direction or guidance in the specification regarding same (e.g., what sequences or structural requirements are necessary to maintain the precise functional characteristics of the polypeptides embraced by the claims), the lack of working examples to use of all the claimed polypeptides, or a representative number with the same , the state of the art showing the unpredictability of function based on structural similarity of proteins, and the breadth of the claims which embrace innumerable variants of *pepducins*, undue experimentation would be required of the skilled artisan to make and use the claimed invention in its full scope.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached at (571) 272-0887.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
4/27/04

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